exposing a tissue of interest in a subject to the agent such that the agent contacts said tissue of interest,

obtaining a test biological sample containing protein from said tissue of interest,

measuring levels of protein markers of toxicity or efficacy in said sample, and

comparing the levels of said markers to the levels of the same markers in a control sample or other sample exposed to known toxic or known effective agents to determine whether the tissue of interest in a subject is experiencing toxicity or an effective response or the degree of such responses, wherein the levels of protein markers determines the relative amount of toxicity or effectiveness.--

REMARKS

Specification support for the amended claims is shown in the following table:

LANGUAGE/CLAIM	SPECIFICATION SUPPORT
" . . . candidate not previously known to have toxicity or efficacy. . ."	Page 24, line 15.
". . . test biological sample . . ."	Original claim 10.
". . . protein levels. . . "	Page 21, lines 6-7.
Claim 5.	Suggestion of the Examiner.
Claim 10.	Grammar correction.
Claim 11.	Grammar correction.

LANGUAGE/CLAIM	SPECIFICATION SUPPORT
" . . . said individual proteins are separated . . ."	Page 4, lines 26-29.
Claim 13.	Grammar correction.
Claim 85.	Page 66, lines 11-13.
Claim 86.	Page 66, lines 11-13.
Claim 87.	Original claim 33.
Claim 88.	Original claim 9.
Claim 89.	Original claim 10.
Claim 90.	Original claim 7.
Claim 91.	Original claim 8.
Claim 92.	Original claim 13.
Claim 93.	Original claim 7 and page 6, line 6 and page 62, line 20.
Claim 94.	Original claim 8.
Claim 95.	Original claims 1 and 9.

Accordingly, no prohibited new matter has been added and entry of the amendments and new claims is requested respectfully.

I. Summary of the Office Action

The Office Action acknowledges the Election of Group I with traverse. Further, the Examiner has rejoined Groups II and III into new Group II, drawn to claims 14-15 and 20-21. Moreover, Groups IV and V have been rejoined into new Group III, drawn to claims 16-17 and 22-23. However, the Examiner maintains that the restriction between new Groups II and III and Groups VI and XXXII is proper and the restriction is made final.

The Title has been objected to for allegedly not being descriptive.

The Specification has been objected to for allegedly (1) failing to define the terms toxicity and efficacy, (2) enumeration of alanine aminotransferase, (3) naming proteins only by MSN and (4) containing potential errors not checked.

The Claims have been objected to for allegedly (1) incorrectly reciting a phrase, (2) claim duplication under 37 CFR §1.75 and (3) characteristics associated with a term.

Claims 1-13 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

Claims 1-8 and 12-13 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Anderson et al (1991).

II. Summary of the Response

Claims 1, 4, 5, 10, 11, 12 and 13 have been amended to more clearly describe the present invention.

The Applicants traverse the outstanding objections and rejections against claims 1-13 as amended and explain why they do not apply to new claims 85-95.

III. **Objections**

(A) The Title has been objected to for allegedly not being descriptive. While not acquiescing to the reasoning offered by the Examiner, and to expedite prosecution toward allowance, Applicants have amended the Title as recited above.

(B) The Specification has been objected to for allegedly (1) failing to define the terms toxicity and efficacy, (2) enumeration of alanine aminotransferase, (3) naming proteins only by MSN and (4) containing potential errors not checked.

(1) The terms efficacy and toxicity are well known and well recognized in the fields of pharmacology, toxicology and medicinal chemistry. Thus, as for specifically defining the terms, no specific definition is needed as the terms are applied with their usual meaning. For example, using "efficacy" as a search term limited to the "spec" field on the USPTO database of issued US Patents, for the years 1996 to 2002, results in 29,751 hits. Further, using the same search strategy for "toxicity" results in 26,017 hits.

Therefore, a requirement for defining said art recognized terms, when such are used in their ordinary meaning, is not proper.

(2) Regarding alanine aminotransferase, while not acquiescing to the reasoning offered by the Examiner, and to expedite prosecution, the specification has been amended (supra).

(3) The use of MSN as generated by the KEPLER® system provides a unique and reproducible identifier for every protein spot on a gel based on pI, MW and abundance data from a predefined Master Spot Pattern. As the KEPLER® system

was available commercially prior to the filing date of the instant application, an identifier generated from said system provides a means such that an MSN would allow for recognition and acquisition of any enumerated protein listed in the instant specification. Some of the spots have been identified as particular proteins. However, because each MSN number is a unique identifier, the name of a particular spot is incidental.

(4) Regarding alleged minor errors that may exist, Applicants will notify/correct any such errors identified.

(C) The Claims have been objected to for allegedly (1) incorrectly reciting a phrase, (2) claim duplication under 37 CFR §1.75 and (3) characteristics associated with a particular term.

(1) Claim 5 stands objected to for reciting the phrase "as a $p<0.1$ [sic]". However, examination of the original claim demonstrates that the phrase as recited reads "as a $p<0.01$." Nonetheless, while not acquiescing to the reasoning offered by the Examiner, the claim has been amended (supra).

(2) Claim 10 stands objected to under 37 C.F.R. §1.75 for allegedly being a substantial duplicate of claim 1.

Claim 10 is differentiated from claim 1 in that the latter recites alternative comparing possibilities, including comparing the test sample markers to control sample markers. Claim 10 narrows claim 1 by requiring a different comparison.

(3) Claim 12 stand objected to for the use of the language "said proteome is prepared by." While not acquiescing to the reasoning offered by the Examiner, and to expedite prosecution toward allowance, Applicants have amended claim 12 (supra).

For these reasons, Applicants respectfully request that the objection against the Title, Specification and Claims be withdrawn.

IV. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-13 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

As claims 7, 8 and 9 have been canceled, the rejection as it pertains to said claims is moot.

Applicants respectfully traverse the rejection against claims 1-13 as amended for the reasons given below.

The Examiner asserts that the "claims . . . directed to a method for determining a degree of toxicity . . ." are indefinite, and then enumerates a list of allegedly indefinite terms as follows:

(a) toxicity,

(b) degree of toxicity,

(c) markers of toxicity,

(c) [sic] efficacy,

(d) markers of efficacy,

(e) to experience toxicity,

(f) to experience an effective response,

(g) to experience the degree of such response.

The terms listed are not *per se* indefinite. For example, the term "toxicity" is not *per se* indefinite as intimated by the Examiner. A brief keyword search for U.S. Patents limited to claims (1996-2002) would show that 422 issued U.S. patents recite the term "toxicity" in the claims. Thus, "toxicity" is a well-recognized term of art. An artisan would well recognize the metes and bounds of the term and of claims containing the term.

The term "degree of toxicity" is not *per se* indefinite as intimated by the Examiner. A brief keyword search for U.S. Patents limited to claims (1996-2002) would show that U.S. Pat. No. 5,933,705 recites the phrase "degree of toxicity" in the claims. Thus, "degree of toxicity" is a well-recognized term of art. An artisan would well recognize the metes and bounds of the term and of claims containing the term.

The term "efficacy" is not *per se* indefinite as intimated by the Examiner. A brief keyword search for U.S. Patents limited to claims (1996-2002) would show that 486 issued U.S. patents recite the term "efficacy" in the claims. Thus, "efficacy" is a well-recognized term of art. An artisan would well recognize the metes and bounds of the term and of claims containing the term. Also toxicity is not efficacy, former may be a factor for determining latter.

With respect to items (e) through (g), the claims recite "experiencing" not "to experience." The inflected form of experience (i.e., experiencing) would only be indefinite if used in a manner repugnant to the ordinary meaning of the term, given that Applicants may be their own lexicographer (*Hormone Research Foundation Inc. v. Genentech Inc.*, 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990)).

The plain meaning of "experiencing" is going through or undergoing. Applicants have not altered this meaning. Thus, when "experiencing" precedes a term that is art recognized, as is the instant situation, holding the phrase indefinite is improper.

Therefore, "experiencing toxicity" is not is not *per se* indefinite as intimated by the Examiner. A brief keyword search for U.S. Patents limited to claims (1996-2002) would show that U.S. Pat. No. 6,335,317 recites the phrase "experiencing toxicity" in the claims. Thus, "experiencing toxicity" is a well-recognized term of art. An artisan would well recognize the metes and bounds of the term and of claims containing the term.

With respect to "markers," respectfully, the Examiner has taken the term out of context. The claims read "protein markers of" not "markers of efficacy" or "markers of toxicity." The specification expressly recites the definition of "protein markers" at page 7, line 30 bridging to page 8, line 4. Respectfully, in view of said definition, the holding that "markers" is in someway indefinite as presented in the Office Action is not proper.

Further, "degree of such response" is not is not *per se* indefinite as intimated by the Examiner. A brief keyword search for U.S. Patents limited to claims (All years) would show that 49 issued U.S. patents recite the term "degree of such response" in the claims. Thus, "degree of such response" is a well-recognized term of art. An artisan would well recognize the metes and bounds of the term and of claims containing the term.

Moreover, "effective response" is not is not *per se* indefinite as intimated by the Examiner. A brief keyword search for U.S. Patents limited to claims (1996-2002) would show that 35 issued U.S. patents recite the term "effective response" in the claims. Thus, "effective

response" is a well-recognized term of art. An artisan would well recognize the metes and bounds of the term and of claims containing the term.

The Examiner further asserts that the term "protein" in claim 1, line 5 is confusing in that "it is not clear which protein Applicants refer to; said biological sample contains thousands of proteins." However, the term "protein" is defined in the specification. Notwithstanding, the term in claim 1, line 5 does not refer to a specific protein (which are called "protein markers," also defined, supra), but in fact refers to generic, total protein. Looking at the claim as a whole, the skilled artisan would understand the metes and bounds of such a claim. As such, the claim is not indefinite.

The Examiner also asserts that claims 2 and 3 recite the term "protein toxicity markers" or "the protein efficacy markers", which are allegedly not defined by the claims or specification. As stated, supra, what is defined in the specification (and is expressly recited in claim 1) are protein markers that are correlative to either efficacy (well recognized term of art, supra) or toxicity (also, well recognized, supra). The terms in claims 2 and 3 are iterations of said terms in claim 1, thus, they have antecedent basis in claim 1. And contrary to the reasoning offered by the Examiner, respectfully, as the terms are defined in claim 1 and are not indefinite, said iterations are not indefinite.

Applicants, respectfully, rebut the intimation by the Examiner regarding limiting the markers to "any protein from Table 8 or 9." The elected claims are directed to a method of using proteins as markers to determine the degree of toxicity or efficacy of an agent. The claimed method is not defined by specific products, but rather by the positive process steps expressly recited.

With regard to claim 4, again the claim must be examined as a whole, not by sequestration of separate terms. Claim 4 specifically recites the measuring of levels of proteins (amount). As such, one of skill in the art would understand the metes and bounds of the claims reciting measuring the level of proteins and increase/decrease with respect to said measuring. However, while not acquiescing to the reasoning of the Examiner, and to expedite prosecution to allowance, Applicants have amended the claim.

Regarding claims 9 and 10, first, claim 10 is not dependent from claim 9. In fact both claims 9 and 10 are dependent from claim 1, so the rejection of claim 10 must be withdrawn as being moot.

With respect to the term "relative amount of toxicity or effectiveness" Applicants would draw the Examiner's attention to page 6, lines 17-28 and page 8, lines 12-19, where "relative" in view of levels and toxicity and effectiveness are clearly explained and exemplified.

Regarding claim 11, the Examiner rejects said claim as being "a literary duplicate of claim 10." Respectfully, claim 10 is dependent from claim 1, while claim 11 is dependent from claim 4. As such, the scope of the two claims is not the same, thus, the claims cannot be "literary" duplicates of one another.

For these reasons, Applicants respectfully request that the rejection against claims 1-13 as amended be withdrawn.

V. Rejection Under 35 U.S.C. §102(b)

Claims 1-8 and 12-13 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Anderson et al (1991).

As claims 7 and 8 have been canceled, the rejection as it pertains to said claims is moot.

Applicants respectfully traverse the rejection against claims 1-8 and 12-13 as amended for the reasons given below.

The Examiner asserts that Anderson et al., by allegedly exposing rat liver tissues to lovostatin or combination of cholestyramine (i.e., known agents) and measuring the levels of proteins markers by two-dimensional electrophoresis, teaches the instant invention as claimed. However, examination of the amended claims and newly added claims demonstrates that the invention as claimed requires the use of an unknown test agent and determining whether said unknown agent has desirable (efficacious) or undesirable (toxic) properties. The measurement of known agents with known properties, as is disclosed in the cited reference, is not identical to the instant method as claimed. Anderson et al. is establishing a standard master pattern and showing that known drugs perturb the protein pattern in an expected way. There is no suggestion that the technique may be used for screening unknown compounds not known or suspected to be efficacious or toxic.

With respect to the new claims, the claimed method requires the measuring of at least one specific marker. Anderson et al. does not demonstrate that any of these markers correlates with the efficacy or toxicity of any unknown agent(s).

As stated in *Hybritech Inc. v. Monoclonal Antibody, Inc.* 802 f.2d 1367, 231 USPQ 81(Fed. Cir. 1986), "It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention."

Therefore, as the cited reference 1) does not require the use of an unknown test agent to determine whether said unknown agent has desirable (efficacious) or undesirable (toxic) properties and 2) does not demonstrate that any of the recited markers are either efficacious or toxic with respect to any unknown agent(s), the method as disclosed in Anderson et al. does not teach the instant method as claimed.

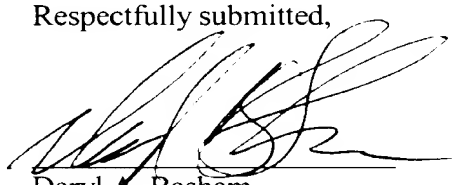
Failure of the cited art to meet every element of the claimed invention does not meet the standard under 102. For these reasons, Applicants respectfully request that the rejection be withdrawn with respect to claims 1-8 and 12-13, and maintain that said rejection does not apply to claims 85-95.

CONCLUSION

Applicants have taken substantial steps to advance prosecution. Reexamination, reconsideration, withdrawal of the rejections and early indication of allowance are requested respectfully. If any questions remain, the Examiner is urged respectfully to contact the undersigned at the local exchange provided below.

The Commissioner hereby is authorized to charge payment of any fees under 37 C.F.R. §1.17 that may become due in connection with the instant application or credit any overpayment to Deposit Account No. 18-2220.

Respectfully submitted,



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Dated: 21 June 2002

Marked-Up Title
for
09 585,475

PROTEIN MARKER[S] INDICATIORS [FOR] OF PHARMACEUTICAL[S] EFFICACY AND [RELATED] TOXICITY

Keratin type II cytoskeletal 8 (MSN 97)

Keratin type I cytoskeletal 18

Keratin type II cytoskeletal 8 (MSN 41)

Hetohexokinase (EC 2.7.1.3)

Lamin b

Major vault protein

Methionine adensyltransferase

3-Mercaptopyruvate sulfotransferase EC 2.8.1.2)

23kD Morphine-binding protein

Nucleolar phosphoprotein B23 (MSN 574)

Nucleolar phosphoprotein B23 (MSN 671)

2-oxoisovalerate dehydrogenase alpha subunit, mitochrondrial

Peroxisomal enoyl hydratase-like protein

Phenylalanine hydroxylase (EC 1.14.16.1)

Protein kinase C inhibitor

Pyruvate kinase, isoenzymes (MSN 282

Pyruvate kinase L

Ras-GTPase-activating protein SH3-domain binding protein

Senescence marker protein-30 MSN 55

Senescence marker protein-30 (MSN 103)

Serine protease inhibitor 2

Tropomysin

MSN 34, MSN 42, MSN 59, MSN 66, MSN 69, MSN 73, MSN 76, MSN 93, MSN 117, MSN 122, MSN 127, MSN 138, MSN 139, MSN 143, MSN 149, MSN 154, MSN 155, MSN 197, MSN 203, ~~MSN 204,~~ MSN 218, MSN 229, MSN 232, MSN 237, MSN 238, MSN 261, MSN 267, MSN 268, MSN 275, MSN 279, MSN 286, MSN 270, MSN 289, MSN 292, MSN 297, MSN 310, MSN 311, MSN 318, MSN 322, MSN 339, MSN 347, MSN 350, MSN 358, MSN 362, MSN 366, MSN 371, MSN 372, MSN 379, MSN 384, MSN 395, MSN 399, MSN 416, MSN 422, MSN 423, MSN 427, MSN 434, MSN 435, MSN 438, MSN 461, MSN 469, MSN 479, MSN 492, MSN 497,